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ALLEN, M EXAMINER

18N2/0713
FINNEGAN, HENDERSON, FARABOW, GARRETT
AND DUNNER
1300 I STREET, NW
WASHINGTON, DC 20005-3315

ART UNIT	PAPER NUMBER
1812	22

DATE MAILED: 07/13/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3/25/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 16-30 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 16-30 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claim 11 has been canceled. Claims 14-15 have been newly added. Claims 6-9 are withdrawn as being drawn to a non-elected invention. Claims 1, 10, and 12-15 are currently under consideration by the examiner.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 2 December 1992 have been fully considered but they are not deemed to be persuasive.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

The specification does not describe nor enable a method for producing and isolating human insulin from the intermediate for mono-Arg insulin (formula I) that occurs in one vessel without having to isolate mono-Arg insulin. In example 4, the fusion protein intermediate is isolated and then mono-Arg insulin is formed. The mono-Arg insulin is isolated. Mono-Arg insulin is treated with carboxypeptidase B to form insulin which is then isolated. Neither the reactions nor the isolation of insulin occur in one vessel and isolation of mono-Arg insulin is required. In example 8, intermediate for mono-Arg insulin (formula I) is purified from the fermentation supernatant. The intermediate is treated with trypsin and mono-Arg insulin is

formed and isolated. Mono-arg insulin is treated with carboxypeptidase B and insulin to form insulin which is then isolated. Neither the reactions nor the isolation of insulin occur in one vessel and isolation of mono-Arg insulin is required.

It is noted that the preamble to claim 11 upon which claim 13 formerly depended is not the same as that of claim 12 upon which claim 13 now depends.

The specification does not describe nor enable preparation of mono-Arg insulin from the intermediate for mono-Arg insulin (formula I) involving cleaving the compound of formula I with cyanogen bromide. It is noted that the specification describes use of cyanogen bromide on a fusion protein not the compound of formula I. (See example 4.)

Claim 13 and 14 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim 1 is rejected under 35 U.S.C. § 103 as being unpatentable over either Markussen et al. (U.S. Patent No. 4,916,212) or Markussen et al. (EPO 163,529).

This rejection is maintained essentially for reasons of record.

Markussen et al. ('212) specifically suggests Thr for X and Arg for Y in column 2, line 64, through column 3, line 18 for the

insulin variant B(1-29)-X_n-Y-A(1-21) produced recombinantly in yeast. "X" is a peptide chain with n amino acids, "n" is an integer from 0 to 33, and Y is Lys or Arg. X is preferably selected from the group consisting of Ala, Ser, and Thr. Rather than a vast number of species, these specific suggestions limit the number of embodiments encompassed.

With respect to claim 1, applicant is claiming a product and the method of production is not stated in the claim nor is it relevant.

The expectation of successfully producing the claimed compound would have been high given that both of changes from the specific embodiment produced by Markussen et al. are conservative amino acid substitutions and both of these changes are to the amino acids found in human insulin.

Claims 12 and 15 are rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (U.S. Patent No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Balschmidt et al. (U.S. Patent No. 5,164,366).

Both Markussen et al. references are applied as in the prior Office action and above.

Balschmidt et al. discloses production of human insulin analogues. The patent discloses that insulin precursors may be converted to insulin by enzymatic cleavage, for example, with trypsin. (See column 7, lines 50-53, and examples.)

It would have been obvious to take the DNA sequence of Markussen et al. and encode Thr at amino acid position 30 and Arg instead of Lys, produce the insulin precursor in yeast as taught by Markussen et al. and convert it to insulin by the method taught by Balschmidt et al. The techniques for enzymatic cleavage using trypsin for the conversion of an insulin precursor would have been well known in the art. One would have been motivated to produce this intermediate for the advantages taught by Markussen et al. and convert it to insulin for the reasons disclosed by Balschmidt et al. and Markussen et al. (See also Markussen et al. claim 29.)

With respect to the methods of claims 12 and 15, it is noted that the method of production is not limited to production in one vessel or a "one-pot reaction." As such, applicant's arguments as to the advantages of this method are moot.

Claim 14 is rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (U.S. Patent No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al.

In light of the new matter rejection above, it appears that applicant intended this claim to be directed to a fusion protein and not the compound of formula I. This art rejection is premised upon this assumption.

Both Markussen references and Goeddel et al. are applied as in the prior Office action and above.

It would have been obvious to take the DNA sequence of Markussen et al. and encode Thr at amino acid position 30 and Arg instead of Lys as taught by Markussen et al., produce the insulin precursor in E. coli as a fusion protein as taught by Goeddel et al., cleave away the protective peptide using cyanogen bromide as taught by Goeddel et al. and then convert it to mono-Arg insulin. The techniques for enzymatic cleavage of fusion proteins using cyanogen bromide and for the conversion of an insulin precursor to mono-Arg insulin would have been well known in the art. One would have been motivated to produce this intermediate for the advantages taught by Markussen et al.

With respect to the method of claim 14, it is noted that the method of production is not limited to production in one vessel or a "one-pot reaction." As such, applicant's arguments as to the advantages of this method are moot.

Claim 10 is rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (EPO 163,529) or Markussen et al. (U.S. Patent No. 4,916,212) either in view of Goeddel et al. (EPO 055,945).

This rejection is maintained for reasons of record. Applicant has not shown any unexpected results for the claimed fusion protein.

The remarks regarding the Markussen et al. references have been addr ssed above.

Claim 10 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited as described below. See M.P.E.P. §§ 706.03(n) and 706.03(z).

This rejection is maintained essentially for reasons of record as applied to claims 10, 11, and 13 in the prior Office action for those portions concerning claim 10 and fusion proteins. There is no evidence that C-terminal fusions with insulin are operative.

It is noted that this rejection has been obviated with respect to claim 11 by its cancellation and that this rejection has been superseded with respect to claim 13 by the new matter rejection above. Claim 13 is not deemed to be enabled by the specification as discussed above and applicant's arguments are not persuasive.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Vertesy et al. (U.S. Patent No. 5,149,716) discloses modified insulin derivatives.

Dorschug (U.S. Patent No. 5,177,058) discloses and claims mono-Arg insulin and other insulin derivatives.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time

policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is (703) 308-0666.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ROBERT J. HILL, JR.
SUPERVISORY PATENT EXAMINER
GROUP 1800